American Journal of Pharmacy

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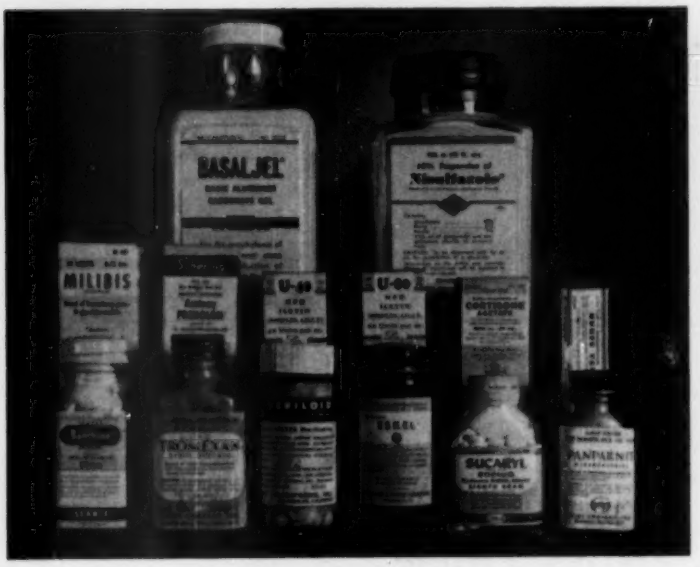

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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CONTENTS

EDITORIAL

PROGRESS AND SELF-DISCIPLINE

WITH this issue we begin a comprehensive review article on recent developments in the field of medicinals.

When one reflects on the changes which have taken place during the last two decades one wonders how the physician, twenty or thirty years ago, was able to function. The truth is, of course, that he was not nearly so well prepared as he is today to serve his patients. Lowered mortality figures and the great increase in life-expectancy give ample evidence of this fact.

The pharmaceutical industry may well be proud of its contributions to human welfare, health and happiness. New medicinal agents, developed largely through its efforts, account for most of the progress made by the medical profession. The practice of medicine with only the drugs of 1900 would today indeed be a nightmare, in spite of the views of a few therapeutic nihilists who still may be found in the profession.

The advances which have been made by the pharmaceutical industry are in no small part due to the individual initiative and highly competitive nature which characterizes the industry. While it is true that government fostered much research during the war years, the research was conducted largely in private laboratories with the competitive spirit still in evidence, even though there was a general sharing of results and teamwork.

Since the war the development of new drugs has not abated. If anything, the tempo has increased and continues to increase. A number of notable discoveries have resulted which are of primary importance as well as extremely profitable. One has only to think of such drugs as chloramphenicol, aureomycin, B_{12} and cortisone which, although relatively new, are used in tremendous amounts. With such "finds" as an incentive, researchers labor diligently hoping to contribute still another to the impressive list. Many valuable drugs have been released in recent years which have not received the professional

or public attention which they merit. This is simply because the list is topped by such extraordinary drugs as mentioned above. There are literally dozens of drugs developed in the last decade which, if released in the twenties, would have brought their discoverer international acclaim. While their application may not be broad they are just as specific and just as important to the patient needing such therapy as the more widely heralded wonder drugs.

As with all things human there is a "seamy" side to all this progress and glamour and we would be closing our eyes to a serious fault were we not to mention it. Some of our companies in the pharmaceutical field are attempting to capitalize on the credulity and confidence of the medical profession by releasing drugs, usually combinations, for which there is little if any excuse, except financial exploitation. Almost every day there comes to our desk some new "trick" combination with an even "trickier" name which, according to the literature, is the last word in therapeutic achievement. Most of these products represent a combination which any pharmacist could prepare and at a price far lower than that at which the proprietary product is listed. These "products," if they justly deserve the name, do not originate with some need in mind. They are simply a means of high pressure detailing to the distraction of the physician and the despair of the pharmacist. The shelves of pharmacy are loaded with such products thus contributing to excessive inventory, increased prescription costs and increased cost of medical care to the public.

Pharmacists are well aware of this vexing problem but it continues in spite of their criticism. Far too many manufacturers adopt a cold attitude toward the individual pharmacist and some have even gone so far as to state that if the physician can be led to prescribe a drug the pharmacist must stock it so why worry about the pharmacist's wishes or welfare? Such a narrow minded opinion is difficult to comprehend. The retail pharmacist is an essential part of the drug distribution system. He is, so to speak, the fingers on the hand of the drug industry. He is, also, a power to be reckoned with in his influence on both physicians and the public and, although inclined to endure calumny, there is a limit to his endurance.

We have and will continue to serve as protagonists for the great American drug industry but this is one weakness which could be and should be corrected by voluntary self-discipline. The industry now enjoys a public and professional esteem far beyond its wildest dreams of fifty years ago. A little restraint here and there in the conception

and release of proprietaries would go far in improving the industry's relationship with pharmacists and it would help maintain the prestige and confidence which the industry enjoys among physicians.

Those who may oppose this viewpoint will doubtless argue that the present situation is a part of the free enterprise system. To this argument we answer—irresponsible exploitation, if unchecked, has and will again spell disaster for free enterprise.

L. F. Tice

CURRENT TRENDS IN MODERN MEDICINALS

By Madeline O. Holland, D. Sc.*

THIS annual review of progress in the various fields related to public health is intended to reflect the progress in new drugs and technics. Although many of the compounds described may still be undergoing animal experimentation or preliminary clinical trials, the results of which may lead to their abandonment, they are included because they are indicative of possible present and future trends.

Wherever feasible the new advances are considered under the group signifying their major action or use. Since there are so many classifications they are presented alphabetically.

ADRENERGIC BLOCKING DRUGS

SY-2

Under investigation is a new adrenergic blocking drug, N-ethyl-N-(2-chloroethyl)-benzhydrylamine hydrochloride. It is similar to Dibenamine in potency, duration of action and specificity. It is practically devoid of antihistamine and anti-acetylcholine properties.

Animal experiments have shown that this drug has a low oral acute toxicity in mice. Comparatively small doses reduced the toxicity of epinephrine in mice and moderate doses failed to diminish histamine-induced bronchiospasm in guinea pigs. In intravenous doses of 5.0 to 20.0 mg./Kg. the drug induced epinephrine reversal, prevented pressor responses to anoxia and definitely reduced pressor responses to splanchnic stimulation in dogs. In cats, doses of 20.0 mg./Kg. intravenously induced epinephrine reversal and diminished or blocked responses of the nictitating membrane to injections of epinephrine and stimulation of the cervical sympathetic nerves. This new agent known as SY-2 is under investigation by Parke, Davis and Co., Inc.

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* Editor, American Professional Pharmacist; Technical Editor: Medical Times, El Farmaceutico and Pharmacy International.

ALCOHOLISM

Hormones

The alcoholic has been considered for sometime to be a psychiatric problem. However, a recent study of two thousand acute and chronic alcoholics by Smith of New York University—Bellevue Medical Center has revealed either improper stimulation or deficiency of the adrenals and sex glands. In alcoholism the pituitary does not produce sufficient hormone to stimulate the adrenals and sex glands resulting in uneasiness and tension. This, in turn, leads to drink. Administration of ACTH and cortisone, sex hormones and ACE (adrenal cortical extract) and vitamin C have brought about response in twenty-four hours.

ANALGESICS

Nisentil

A new obstetrical analgesic, 1,3-dimethyl-4-phenyl-4-propionoxypiperidine hydrochloride (*dl*-alpha form), has recently been made available. Its action resembles that of morphine. For optimum results it should be given subcutaneously in doses of 30 mg. When given both orally and subcutaneously a lesser percentage of good results was obtained. When compared with morphine, methadone and combinations of morphine with neostigmine or scopolamine it appeared to produce a greater percentage of good results. Under the name of Nisentil this analgesic is being marketed by Hoffmann-La Roche, Inc.

Subdamine

Another new analgesic and sedative is being investigated particularly for its properties in relieving the symptoms of anxiety and tension in psychoneurotic patients. It is of value as well in certain organic diseases such as hypertension and the climacteric.

Chemically, this new drug is 1-diethylcarbamylpiperazine. It possesses potent sedative activity but low somnifacient activity. Its toxicity also is low.

Sixty-three of 83 patients (76 per cent) treated with this drug reported improvement to some degree. Eighty-six per cent of 66 patients with functional manifestations predominating showed some relief of symptoms. Small doses of phenobarbital achieved about the same results but in some cases it produced drowsiness which does not occur with the new drug.

The only side reactions observed were mild disorientation at night, nausea, dizziness and vomiting. The first mentioned was the only severe reaction, the others occurring in only a few patients.

This new analgesic is known as Subdamine and is being investigated by Lederle Laboratories Division, American Cyanamid Company.

ANESTHETICS

Procaine Derivatives

The ortho-substituted para-aminobenzoates and some of their analogs have been synthesized and tested for their activity as local anesthetics. The two most active local anesthetics in use at present are tetracaine and dibucaine and certain of the aforementioned procaine derivatives appear to be even more potent. A substantial increase in activity was produced by substituting an ortho-hydroxy group in procaine. Only a slight increase occurred when an ortho-methoxy group was substituted. However, the activity is increased considerably as the size of the ortho-alkoxy group increases. The ortho-hexyloxy compound is approximately 100 times as active as procaine. Tests for toxicity have shown that it is proportional to the activity and based on the activity these compounds are less toxic than procaine. The only exception is the ortho-methoxy compound. The ortho-alkoxy derivatives of procaine apparently are less irritating locally since this effect does not seem to have any direct dependence upon activity or toxicity. A good activity irritation ratio is exhibited by the most active compounds. The ortho-propoxy analog has an activity of about 10 times that of procaine but it is only twice as irritating. These compounds are being studied by the Sterling-Winthrop Research Institute.

Surital Sodium

In all fields of medicine the search goes on for the ideal drug for some specific use. Just so in the field of anesthesia, it is thought that the barbituric acid derivatives now employed parenterally do not entirely meet the specifications of the ideal agent. Consequently, a new drug, sodium 5-allyl-5-(1-methylbutyl)-2-thiobarbiturate, is being evaluated. The drug was given by intermittent intravenous injection of a concentrated (2-2.5 per cent) solution and by continuous intravenous drip of a dilute solution (0.3 per cent). Smooth, rapid

induction occurred when 3 to 10 cc. (60-250 mg.) of the 2.5 per cent solution was given preceding inhalation anesthesia.

The new drug was tested on 1200 patients and was used in the following ways: for the induction of general anesthesia; for induction and endotracheal intubation; with regional anesthesia; for complete maintenance of anesthesia with nitrous oxide-oxygen; with curare; and in anticonvulsant therapy. Encouraging results were observed when it was administered rectally to children.

Although this new drug does not necessarily meet the ideal requirements, it does have certain advantages such as rapid awakening from a comparable plane of anesthesia, more rapid restoration of spontaneous breathing following large doses administered rapidly, less frequent circulatory depression when given in equivalent doses and the more benign character of the laryngospasm.

Known as Surital Sodium this new agent is being investigated by Parke, Davis and Co., Inc.

ANTIBIOTICS

Antimycin A

One of the newer antibiotics discovered recently is known as Antimycin A. It is a crystalline substance which was isolated from an unidentified species of *Streptomyces*.

Chemically it appears to be an optically active, nitrogenous phenol having the molecular formula $C_{28}H_{40}O_9N_2$. When tested on certain phytopathogens this antibiotic, known as Antimycin A, was found to possess potent fungicidal properties. At dilutions as high as 1:800,000,000 it produced inhibitory effects against *Nigrospora sphaerica* (Sacc.). Because of these properties preliminary tests of its insecticidal and miticidal potentialities have been carried out.

It is not a contact poison for insects but must be ingested to act. In the tests common houseflies, *Musca domestica L.*, sprayed with 10 p.p.m. of antimycin A showed no harmful effects. However, when a ball of absorbent cotton was saturated with water containing 10 p.p.m. of the antibiotic and placed in a container with 38 per cent of the flies they were killed in 24 hours after feeding on the cotton. Similar results were reported when antimycin A was tested against the large milkweed bug, *Oncopeltus fasciatus* (Dall.). Other insects, however, were not affected. The German cockroach, *Blatella ger-*

manica (L.), when given the same concentration of drug, was not affected.

Tests with wool fabric revealed that the larvae of the webbing clothes moth, *Tineola biselliella*, (Hum.) ate the test swatches with impunity whereas the feeding of the black carpet beetle, *Attagenus piceus* (Oliv.), was inhibited. In comparison tests with aluminum silicofluoride, commonly used for protection of fabrics, antimycin A was found to give the same degree of protection at 1/100 of the concentration of the silicofluoride. Antimycin A apparently repels the larvae since none of those exposed to the impregnated wool was dead after 28 days exposure. Further tests with Coleoptera such as the Mexican bean beetle larvae, *Epilochna varivestis* Muls., revealed an effect on this species. However, no effect was observed on the Lepidoptera as represented by the Southern army worm, *Prodenia eridania* (Cram.). This latter worm ate lima bean leaves, which had been treated with antimycin A, without any harmful effects. When compared with methoxychlor, which is currently used to control the Mexican bean beetle, antimycin A, in concentrations of 25 p.p.m. was as effective as 500 p.p.m. of the former compound.

Antimycin also is effective against the red spider mite, *Tetranychus* sp. Di(p-chloro-phenyl) methyl carbinol or DMC is now used against this mite. When compared with antimycin A the latter appears to be 3 or 4 times more effective.

Thus the new antibiotics being discovered almost daily may prove useful to man in other ways than in curing disease.

Diplomycin

First isolated from a Diplococcus in 1945 by Noster, diplomycin is now being tested in the surgical clinic of AArhus Kommunehospital, Copenhagen in the treatment of 150 patients with different infectious diseases. This new antibiotic appears to possess a pronounced antibacterial action on gram-positive and gram-negative micro-organisms and on tubercle bacilli. In addition, bacterial resistance does not develop and therefore it has been shown effective in treating cases in which bacterial resistance to penicillin and streptomycin has developed. It has only slight toxicity. Chronic ulcers of the leg and other localized infections have been treated effectively with diplomycin in ointment form. The clinical effect of intravenous injections of diplomycin filtrates in infections such as abscesses, mas-

titis and osteomyelitis was often equal to that attained with penicillin. In treating *B. coli* infections of the urinary tract its effectiveness was equal to that of streptomycin and in some instances even better. In addition, it did not produce the serious side effects which the latter does.

Fungicidin

Fungicidin is another new antibiotic agent recently isolated. It is extracted by means of alcohols from the surface growth on liquid medium. To date it appears to differ from all other antibiotics. It is effective *in vitro* against a large number of nonpathogenic and pathogenic fungi, including *Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, Paracoccidioides brasiliensis, Trichophyton rubrum* (*purpureum*), and *T. mentagrophytes* (*gypseum*). In higher concentrations it has not shown much activity against some of the common bacteria such as *Staphylococcus aureus, Salmonella paratyphi B, S. typhosa, Shigella paradysenteriae,* and *Bacterium coli.* Because of the unusual activity *in vitro* fungicidin is being investigated for possible therapeutic value in the Division of Laboratories and Research of the New York State Department of Health.

Hydroxystreptomycin

Hydroxystreptomycin has been isolated from a new species of *Streptomyces* found in Japanese soil. Because the aerial mycelium changes slowly from grayish white to a flesh color this species has been given the name, *Streptomyces griseocarnus N.* sp.

The antibiotic prepared from it is purified in the same manner as is streptomycin. It has been named hydroxystreptomycin because of its composition and the nature of its degradation products. It resembles streptomycin in composition, optical rotation and biological potency. The analytical figures and x-ray diffraction pattern of the two helicanthates are almost identical. The naphthalene-β-sulfonates of both substances show similar melting points and x-ray patterns as well. Differentiation of the new compound from streptomycin was made by means of paper strip chromatography. The trihydrochloride of hydroxystreptomycin when assayed against *Bacillus subtilis,* was found to be equivalent to 784 micrograms of streptomycin base per

milligram. For streptomycin trihydrochloride the corresponding value is 842 micrograms per milligram.

It is hoped that animal experiments and clinical studies will reveal that this compound does not possess the disadvantages of streptomycin.

Lupulon

The search for the ideal drug in tuberculosis therapy continues. Another new antibiotic, has been shown to have some effect in this disease. It is currently being studied at the University of California Medical Service, San Francisco Hospital, San Francisco Department of Public Health and the Div. of Pharmacology and Experimental Therapeutics, Univ. of California Med. School, San Francisco, Calif. under a grant from Eli Lilly and Co. Given the name lupulon, it is one of the two antibiotics derived from the soft resins of hops, *Humulus lupulus*.

It is a colorless, odorless and tasteless crystalline substance. It is soluble in water to the extent of 12 mg./L. at a pH of 5.9. The melting point is 88 to 92° C. It is lipoid soluble, unsaturated and sensitive to oxidation.

When tested on mice it was found that one-tenth of the acute LD_{50} could be given intramuscularly every day for 4 weeks without gross evidence of harmful effects. When the tissues of the mice were examined histopathologically small areas of leukocytic infiltration in the liver and foci of degeneration in the renal tubules were observed.

In vitro and *in vivo* tests showed promising effects by lupulon on tubercle bacilli. From these observations it was thought that lupulon might have some effect on tuberculosis in humans. Its greater solubility in lipoids might allow for greater penetration of the waxy coat of the mycobacteria.

The 10 patients selected were from both sexes and varied in age from 25 to 43 years. Of the 10, 9 had moderately advanced pulmonary tuberculosis and one had tuberculous laryngitis. One had minimal tracheobronchial disease in addition to the pulmonary disease.

The antibiotic was given in gelatin capsules each containing approximately 0.5 Gm. It was administered orally in 1 Gm. dosages every 4 hours from 6 A. M. to 10 P. M. so that each patient received 5 Gm. daily regardless of weight. Five patients were given the drug for 3 months, 1 for 2 months, 2 for 50 days and 2 a week or less.

Development of complications or side reactions necessitated discontinuing the drug in the last 4 patients.

Blood level tests revealed detectable amounts of the antibiotic in 7 patients tested at regular intervals for a period of 8 weeks. The levels varied from 1.9 to 6.5 mcg. per ml. These values were beyond the range of the sera obtained from untreated patients.

All of the patients were examined throughly and all of the standard tests were conducted. In 3 patients treated with lupulon there were observed significant decreases in the daily volume of sputum and in the frequency and intensity of the cough. Three patients lost 5½ to 9 pounds whereas the others did not change weight to any significant extent. X-ray examination revealed signs of improvement of the pulmonary lesion in 1 patient. In the others no observed changes could be credited to the medication. No hepatic or renal function alterations occurred as a result of therapy. Electrocardiograms also revealed no changes.

Three patients developed a negative sputum after therapy but the rest showed little change. No signs of toxicity to the liver, kidney, bone marrow or myocardium were observed.

However, there was a certain amount of gastro-intestinal irritation caused by the antibiotic. There was an epigastric sensation of burning and lower abdominal cramping which developed within 5 minutes to 6 hours after the first dose. Watery diarrhea sometimes accompanied these symptoms and it could not be completely controlled by bismuth subcarbonate or other agents. Some patients experienced nausea and vomiting which continued for 2 days to 1½ weeks. In 2 patients therapy was stopped because of the severe gastrointestinal disturbance. After the symptoms stopped the patients continued to have a mild loss of appetite. Transient mild frontal headaches were experienced by two patients and lightheadedness by 2 others. Slight somnolence was observed by 2 patients. One patient developed an erythematous macular rash which lasted 2 days and a generalized myalgia for 5 days. Transient eosinophilia was observed in 2 other patients.

Although these investigations are only in the preliminary stages and no definite conclusions can be drawn the results observed are sufficiently encouraging as to lead to further studies. The possibility of drug resistance is now being investigated. However, until more is known about lupulon it should not be used in treating tuberculosis except for investigative purposes.

Nemotinic Acid, Nemotin

Nemotinic acid and nemotin are antibiotics which have been isolated from culture liquids of *Poria tenuis, Poria corticola,* and an unidentified Basidiomycete from white cedar ("fungus B-841"). They differ markedly in their antifungal action. However, they have shown effects against *Mycobacterium tuberculosis.*

Netropsin, Thiolutin

At a recent meeting of the American Chemical Society two new antibiotics were reported. One, named netropsin, was obtained from culture broths of an actinomycete, *Streptomyces netropsis.* It is very active *in vitro* against a wide spectrum of organisms. Unfortunately, animal tests have shown that it is sufficiently toxic as to possibly limit its usefulness. However, it has shown activity against clothes moth larvae and the black carpet beetle. Netropsin is believed to be a tetra-acidic base with an empirical formula of $C_{32}H_{48}N_{14}O_4$. In acid solution it is relatively stable but in alkaline solution it is unstable.

The other new antibiotic reported at the same meeting is thiolutin, isolated from strains of *Streptomyces albus.* It inhibits gram-positive and gram-negative bacteria as well as fungi. Charles Pfizer and Co. is investigating these two antibiotics.

Prodigiosin

Botts and Lack of the Birmingham Veterans Administration Hospital, Van Nuys, California, have reported that a dye, extracted from bacteria, *B-prodigiosus,* is effective *in vivo* and *in vitro* against the highly infectious San Joaquin or valley fever called coccidioidomycosis. The new antibiotic is named prodigiosin.

Synergism

Synergism between drugs is not new, by any means. However, during the past year synergism between various antibiotics and between antibiotics and other drugs has been reported. Penicillin and bacitracin have been shown to be more effective than either antibiotic alone in certain diseases such as subacute bacterial endocarditis. It is believed to be the first between antibiotics to have been reported. It is considered to be a true synergism in that the two can be given

in smaller quantities than are curative for either drug alone but together they effect a cure.

The synergistic effects of bacitracin and penicillin were demonstrated first on rabbits infected with *Treponema pallidum*. It was found that the curative dose of bacitracin was about 9000 units/Kg. and that of penicillin was 30-40 mg./Kg. When given together cure was effected with as little as 1 mg./Kg. of penicillin and 1,280 units/Kg. of bacitracin. Thus the synergistic effect of the two antibiotics resulted in a need for only 1/40th as much penicillin and 1/7th as much bacitracin. An increase in the penicillin dosage to 1 to 4 to 16 mg./Kg. reduced the dosage of bacitracin further from 1280 to 840 to 480 units/Kg.

In vitro experiments with 18 strains of alpha and gamma hemolytic streptococci also revealed a synergistic effect. This effect also has been reported in *in vitro* experiments and clinically *in vivo* with numerous strains of staphylococci, *Cl. welchii* and occasionally with hemolytic streptococci.

This phenomenon will undoubtedly prove to be of value in cases where the organism is resistant to penicillin but sensitive to bacitracin. Either antibiotic alone in moderate doses in such instances would probably be ineffective in controlling the infection.

Clinical trials are now underway to determine the possible uses of this synergistic effect. Representative cases already reported include a streptococcal infection which did not respond to 300,000 units of penicillin daily. This dosage was increased in 3 days to as high as 1,200,000 units and continued for 6 days. The temperature still was elevated and the blood culture was positive. Administration of 1,200,000 units of penicillin and 6,000 units of bacitracin (divided into 3 equal doses) daily resulted in negative blood cultures in 10 days. In an infection caused by an enterococcus type of streptococcus which did not respond to penicillin negative blood cultures were achieved in 6 days by supplemental doses of 6,000 units of bacitracin daily. A combination of penicillin and bacitracin known as Penitracin will be marketed by C. S. C. Pharmaceuticals, Division of Commercial Solvents Corporation.

Penicillin and dihydrostreptomycin have been combined for their synergistic effect in the treatment of mixed infections due to gram-positive and gram-negative organisms such as subacute bacterial endocarditis, urinary tract infections; and also in the preparation and protection of surgical sites.

In a study of the effects of the two drugs together it was revealed that the combined effect on enteroccoci is greater than a summation of the effects of the individual drugs. Streptomycin, in the concentrations employed, had no effect and penicillin was in the optimal zone for the organism so that no increase in concentration would be of any value. Thus the increased effect must be a true synergism. The rapid sterilization of the medium (rapid death of the organisms) is indicative of at least tenfold potentiation of penicillin action by streptomycin.

The next question which arises is whether the viable enterococci remaining after treatment with penicillin alone are resistant mutants and, consequently, are able to multiply. If this is so, then the streptomycin when mixed with penicillin is simply affecting penicillin-resistant organisms. Experiments along these lines revealed that this is not the case. The streptomycin-penicillin synergism on enterococci increases the bactericidal rate beyond that which can be obtained with penicillin alone. Procaine penicillin, sodium penicillin and dihydrostreptomycin for parenteral administration are available as Combiotic from Charles Pfizer and Co., Inc. and as Penicillin Dihydro from Parke, Davis and Co.

When the therapeutic effect of PAS given orally was compared with that of streptomycin given subcutaneously the latter was found to be 3 to 6 times more active. When both were given subcutaneously streptomycin was five times more active.

Unfortunately, although streptomycin is more potent, the organisms do develop a resistance to it whereas with PAS this does not occur. Once the resistant organisms develop therapy with streptomycin is ineffective. It is generally agreed that 50 to 70 per cent of the patients who continue to discharge tubercle bacilli after 120 days of therapy will have streptomycin-resistant strains. In a large series of patients studied by the Veterans Administration about 60 per cent of the positive cultures from patients treated for 3 months showed resistance *in vitro* to 10 or more micrograms of streptomycin per ml. of medium. This resistance to the human type H 37 Rv was retarded when diaminodiphenylsulfone was added to the medium. When streptomycin and sulfathiazole were used the resistance of the avian tubercle bacillus and *M. ranae* also was retarded.

Thus it appeared obvious that streptomycin should be used along with other antituberculous agents in order to delay or prevent the development of streptomycin-resistant strains.

In a series of patients with tuberculosis, PAS, Promin and streptomycin were given in combination. The PAS was given orally in the maximal tolerated dose (5 to 10 Gm.). The streptomycin was given in doses of 0.5 Gm. twice daily intramuscularly to some, and 0.5 Gm. once daily to others. Promin was given in daily dosage of 5 Gm. intravenously for the first 14 days of a 21 day period. No evidence was observed that any of the drugs increased the toxicity of the others.

By means of cultures the organisms were studied for resistance. At the end of three months of therapy only one patient showed streptomycin-resistant tubercle bacilli and 3 additional patients developed these during the sixth months of therapy. These results appeared promising and led to further studies.

A study of the combined therapy of PAS and streptomycin in guinea pigs has shown that the two drugs produce a therapeutic effect better than that produced by either drug alone in the same doses and that the results of this combined therapy are comparable to those obtained with streptomycin alone. Thus it appears possible to give, along with PAS, smaller doses of streptomycin than would be given alone and in this way the hazard of toxic effects is reduced and the development of resistant forms delayed. Dihydrostreptomycin may be used instead of streptomycin. Thus the hazard of toxic effects is further reduced. However, the possibility of resistant forms developing is not diminished.

Recently penicillin has been made available in combination with the three sulfonamides: sulfamerazine, sulfadiazine and sulfamethazine for simultaneous treatment of infections where oral administration of penicillin and the sulfonamides is indicated. This combination is recommended for treatment of pneumonia, gonorrhea, mastoiditis, scarlet fever and urinary tract infections and as a prophylactic measure before and after tooth extraction, tonsillectomy, cesarean section and minor surgical procedures. This product is being marketed in tablet form as Neotrizine by Eli Lilly and Co., Inc., as Pentresamide by Sharp and Dohme, Inc., as Eskacillin-Sulfas by Smith, Kline and French Laboratories and as Dram-Cillin with Triple Sulfonamides by White Laboratories, Inc. The Upjohn Co. is making available Biosulfa which combines penicillin, sulfadiazine, sulfamerazine and calcium carbonate for many of the same indications.

This synergistic effect of antibiotics for each other, however, cannot be taken for granted. Some, when given together may be

less effective than one alone or even neutralize each other. In experiments on enterococci with chloramphenicol alone in concentrations of 10 mcg./ml. no significant effect was observed. Although there was a noticeable effect when this concentration of chloramphenicol was mixed with 6 mcg./ml. of penicillin further tests revealed that it was less than with penicillin alone. It required 6 to 12 days with the penicillin-chloramphenicol mixture to achieve the same low number of viable enterococci obtained with penicillin alone in 24 hours. From these experiments it could be assumed that chloramphenicol in some way inhibited the bactericidal effects of penicillin on enterococci. This antagonistic action was observed with varying concentrations of both antibiotics and in varying degrees with all nine strains of enterococci.

Another interesting observation of these studies was that the chloramphenicol-penicillin mixture caused a slow but steady decrease of the bacterial population whereas penicillin alone resulted in a great increase after the sharp decline originally observed. Thus the mixture was equal to high concentrations of penicillin such as 300 mcg./ml. However, the number of viable bacteria decreased more slowly with the mixture and with high concentrations of penicillin than they did at the optimal concentration of penicillin alone (6 mcg./ml.) and all the enterococci were killed after long periods of incubation. Thus it was shown that not all of the antibiotics are synergistic in action but that some may be antagonistic.

Terramycin

Streptomyces rimosus, another actinomycete, has been isolated from soil and found to produce an antibiotic. The name *rimosus* was given to it because it presents a cracked appearance when growing upon the surface of agar medium. Growth of test organisms was inhibited in the vicinity of *Streptomyces rimosus* when it was grown on plates containing nutrient agar and when it was grown under submerged aerobic conditions the broth showed inhibitory effects. A crystalline antibiotic was isolated from the broth cultures. Because of its derivation it was named terramycin.

Terramycin is amphoteric and is capable of forming both a crystalline hydrochloride and a sodium salt. It melts with decomposition at approximately 185° C. It is soluble in methanol, ethanol, acetone and propylene glycol. In water 0.25 mg. may be dissolved per ml. at

25° C. It is insoluble in ether and petroleum ether. One outstanding advantage in its properties is that it is stable over long periods of time in aqueous solutions at an approximate pH of 2.0 to 5.0, at room temperature.

A terramycin unit is defined as one microgram of the pure anhydrous amphoteric compound. The activity is expressed in terms of the equivalent weight (mcg.) of crystalline terramycin needed to inhibit growth. The activities of the salts of terramycin are stated in terms of the equivalent weight of pure amphoteric terramycin.

Terramycin is a relatively non-toxic antibiotic as shown by extensive animal studies and clinical observations in more than 350 patients. No toxic reactions have been observed when sodium terramycin or terramycin hydrochloride was orally administered to dogs in dosages of 80 to 500 mg./Kg. of body weight. Some toxic symptoms were observed, however, in a small percentage of animals given 80 to 160 mg./Kg. of body weight of sodium terramycin intramuscularly over long periods of time.

Studies of the absorption and excretion of terramycin in dogs and rabbits have indicated that it is absorbed rapidly throughout the body when given orally or parenterally. It is excreted in a biologically active form

Studies have indicated (a) that maximum concentrations of terramycin may be detected in the serum of most patients receiving single oral doses of 25 to 50 mg. of terramycin hydrochloride per Kg. of body weight, within 2 hours after administration; (b) that the maximum concentrations achieved after administration of such doses are 5 to 6 and 10 to 20 mcg. per ml. respectively; (c) that after maximum serum concentrations are attained, the levels remain at a plateau for 2 to 4 hours and then decline; (d) that the drug is present in high concentrations in the urine within 2 hours after administration.

Mild gastrointestinal disturbances have been observed in a small percentage of patients. Looseness of the stools was the most common reaction reported. In some cases there was mild nausea and vomiting which in most instances occurred when the drug was taken on an empty stomach. By administering terramycin just prior to a light meal these reactions usually were avoided. When nausea and vomiting did occur they usually were more severe in the first day or two and then disappeared. It has been suggested that the frequency and severity of these reactions may vary directly with the size of the

daily dose since no such reactions occurred following dosages of 1 to 2 Gm. daily.

Terramycin is indicated in the therapy of diseases caused by many of the gram-positive and gram-negative bacteria, both aerobic and anaerobic; the rickettsiae and certain viruses. At present, the recommended oral dose is 2 to 3 Gm. daily in divided doses given every 6 hours for acute infections. For severe infections double the quantity may be necessary. Adult and children's dosages are the same. Just as with the other antibiotics the dosage in many cases will need to be adjusted for the patient. Therapy should be continued for at least 48 hours after the temperature has returned to the normal level and the acute symptoms have disappeared. All dosages mentioned are in terms of weight of pure terramycin. The intravenous form is indicated particularly in the treatment of peritonitis and in the prophylactic sterilization of the intestines before and after abdominal surgery.

Terramycin is marketed in troches for oral, dental and throat infections, in capsules and an elixir (Terrabon) for oral use. The injectable form known as Terramycin Intravenous is also available from Charles Pfizer and Co., Inc.

The most recent report on this antibiotic reveals that it is of value in treating eye infections such as trachoma; conjunctivitis caused by the pus-forming staphylococcus, sometimes found with other micro-organisms; deep-seated eye troubles, such as ulcers and similar conditions which may occur in areas difficult to get at; a wide variety of infections and inflammations of the conjunctiva, outer eye surfaces, of the tear forming sac, and of the minute passages leading to and from the eye; infections following external eye damage, as well as involvements of the eye in venereal disease. On some severe cases terramycin was given orally as well as topically in an eye drop or ophthalmic ointment. For the preparation of the eye drop the antibiotic has been made available in a dry mixture of the crystalline hydrochloride and a sodium borate-sodium chloride buffer. When dissolved in 5 cc. of Water for Injection, U. S. P., one cc. provides the equivalent of 5 mg. of pure terramycin. The crystalline hydrochloride is also available suspended in a petrolatum base. Each gram contains the equivalent of 1 mg. of pure terramycin. Crystalline terramycin hydrochloride is well tolerated by the mucus membranes and other eye tissues.

Thrombodent Dental Cones

To accelerate firm clot formation and minimize infection following oral surgery there is now available a dental cone containing 1 unit of human thrombin, enough to clot 1 cc. of normal blood in less than one minute, combined with 1 mg. of tyrothricin, which is effective against many of the microorganisms present in the oral cavity that may contaminate postoperative dental wounds. Known as Thrombodent Dental Cones these cones are being marketed by Sharp and Dohme, Inc. Because they are so highly absorbent they are protected from moisture by a desiccant in a pocket at the bottom of the bottle and the new type polyethylene snap cap, an almost perfect barrier to water vapor and air.

Viomycin

More than 100,000 samples of soil have been processed for antibiotic activity but only 84 molds from this group were found worthy of further investigation. Of the 84 it was found that only two possessed sufficient activity as to warrant clinical trial. These were the groups producing terramycin and viomycin.

Viomycin was isolated from a sample of soil obtained in Cuba. At the present it is difficult to make any prediction as to its possible value in humans since the tests have been so limited. In animals viomycin has been shown to suppress tuberculosis. Mice and guinea pigs were used for these protection tests. Viomycin is believed to be effective against streptomycin-sensitive and streptomycin-resistant strains as shown by both *in vitro* and animal tests. This is indeed an important property.

Although further clinical studies are necessary to determine its effectiveness in humans the clinical trials thus far have revealed that it can be given to humans for prolonged periods of time.

Viomycin is being investigated by Charles Pfizer and Co., Inc.

ANTICOAGULANT

Heparinoid

Experiments are now in progress on a new, synthetic anticoagulant, Heparinoid. Chemically it is a polysulfuric ester of polyanhydromannuronic acid obtained as a water-soluble sodium salt which is stable at room temperature. It is prepared by the sulfation of alginic acid.

Eleven patients were selected for the first clinical trials. They were given intravenously a solution of the compound 25 times. The dosage necessary to prolong the clotting time 2 to 3 times was found to be 5-10 mg./Kg. As with most drugs, however, the response varied in some of the patients. Although this dosage is approximately 13 times that of the sodium salt of heparin required for the same effect, the results may be more prolonged since they lasted for 4 to 8 hours. Only 3 patients experienced any toxic reactions and 2 were mild.

Phenylindandione

Another new anticoagulant being tested is phenylindandione. It appears to have an action which is intermediate between those of heparin and dicumarol. However, it resembles dicumarol more closely. The first dose given is 200 mg. followed by 65 mg. dosages daily for maintenance. In different individuals the rapidity of action was observed to vary. The desired prothrombin level was attained in 10 to 20 hours in 18 patients; in 20 to 28 hours in 20; in 29 to 40 hours in 7; and in 40 to 50 hours in 3.

Phenylindandione is known under the tradename of Danilone and is being investigated by Charles Frosst Co. of Canada.

Tromexan

Bis-3′,-(4-oxycoumarinyl) ethyl acetate also known as B. O. E. A. has been shown to have anticoagulant properties. Although it appears to more closely approach the ideal anticoagulant it is four times less active than dicumarol. It is necessary also that all the precautions accompanying anticoagulant therapy be employed. B. O. E. A. is more rapidly eliminated than is dicumarol so that any hemorrhaging should be less severe.

B. O. E. A. has been tested on patients with venous thrombosis, pulmonary emboli, arterial thrombosis, or emboli. The treatment periods varied from five days to ten months. The prothrombin level of the blood was decreased to less than fifty per cent of normal within thirty-six hours in more than eighty per cent. After withdrawal of the drug the prothrombin time again returned to more than fifty per cent of normal within thirty-six hours. No toxic effects were observed.

Spofa (United Pharmaceutical Works), Prague, Pharmaceutical Laboratories Geigy Ltd., Geigy Company, Inc. have supplied B. O.

E. A. under the respective names of Pelentan and Tromexan (Geigy).

ANTIHISTAMINICS

Neovacagen

No attempt will be made in this review to list the myriad of antihistaminic cold preparations since they are all minor variations of one basic type. However, there is one now available which employs a somewhat different principle. This product combines in one tablet an antihistaminic, methapyrilene hydrochloride (25 mg.), and the soluble antigenic substances of approximately 100,000 million bacteria usually associated with infections of the respiratory tract. It is recommended for the stimulation of specific immunity against secondary bacterial invaders in respiratory infections. Not only is this tablet claimed to be of value against the organisms causing the distress in later stages of the common cold but also for preventing the more serious complications which often follow upper respiratory infections. Sharp and Dohme, Inc. is marketing this product under the tradename of Neovacagen.

ANTI-INFECTIVES

Benemid

Research has been directed toward a search for an agent which would enhance the concentration of PAS in plasma. A substance, known chemically as 4′-carboxyphenylmethanesulfonanilide (Carinamide), which is used to enhance the action of penicillin, was tried with PAS. It was found that this chemical also inhibits tubular excretion of PAS. In doing so the renal clearances of PAS are reduced to the glomerular filtration rate. Following this it was also suggested that the same elevated concentrations in the plasma might be achieved by having PAS in a conjugated form when it reaches the kidneys so that the renal tubules would not clear it so readily. This theory was based upon the fact that 4′-carboxyphenylmethanesulfonanilide acts upon an enzymatic conjugase system.

Recently a new chemical, *p*-(di-*n*-propylsulfamyl) benzoic acid, has been shown to effect an enzymatic conjugation system which is believed to be related to the inhibition of excretion of penicillin and *p*-aminohippurate. Consequently, this compound was tested for its effects on PAS as well

Known as probenecid this new chemical is a stable, crystalline white powder nearly insoluble in water. At first the drug is tasteless but some have observed a bitter taste followed by a pleasant aftertaste. It can be given orally since it is absorbed rapidly from the gastrointestinal tract. Plasma concentrations have been observed for as long as 36 hours following one oral dose given to dogs. The plasma proteins bind almost 75 per cent of probenecid. It is excreted almost wholly in a conjugated form (probably a glucuronide) in the urine. A high therapeutic index was revealed by acute and chronic toxicity tests in mice and dogs. No toxicity in humans has been observed after 3 weeks' administration of the drug.

Clinical studies revealed that if given in adequate amounts probenecid will enhance the effects of PAS. Probenecid is believed to inhibit the conjugation of PAS so that it reaches the kidney in a form which is not so rapidly excreted as are the various conjugates of PAS. It is hoped that this compound will aid in increasing the use and efficiency of PAS in the therapy of tuberculosis.

Probenecid under the tradename of Benemid is being tested by Sharp and Dohme, Inc.

Camoquin

Amodiaquin, known chemically as 4(3′-diethylaminomethyl-hydroxanilino)-7-chloroquinoline and supplied as the dichloride dihydrate, is a light yellow, crystalline powder, available in tablets representing 0.2 Gm. of the base. It is highly effective in the treatment of malaria. Adequate dosage results in prompt disappearance of plasmodia from the blood stream and clinical recovery from an acute attack. It is also valuable as a prophylactic suppressive against acute attacks of malaria. For adults, 3 tablets (0.6 Gm.) are usually taken as a single dose. The single dose seems to produce more favorable results than the same or even larger amounts in divided doses.

Under the tradename of Camoquin this new antimalarial is marketed by Parke, Davis and Co.

Combination

The protozoan disease of cows, anaplasmosis, was cured in 5 cows in advanced stages of the disease treated with a combination of Aricyl, an arsenical, and 7-chloro-4-(4′diethylamino-1′-methyl-butyl-amino) quinoline disulfate. Twelve to 15 cc. of the Aricyl were given and

2400 mg. of the quinoline disulfate derivative were given intravenously. Aricyl alone produced recovery in 71 per cent of 17 cows according to Farley, Pearson, Foote, and Kliewer in the *North American Vet.*

Esparseno

Dioxy-diamido-arsenobenzol is being used in the therapy of cutaneous leishmaniasis. It is marketed in 1 cc. ampuls each containing 0.12 Gm. of amino-arseno-phenol and is given intravenously. It is known as Esparseno.

Lutazol, Ophtazol

The sodium salt of para-sulfamido-phenyl-azo-salicylic acid (G33) is being marketed for the treatment of trachoma. Known as Lutazol it is being marketed by Roussel Laboratories in a 2 per cent solution in ampuls and a 0.5 gr. tablet. The lithium salt of the same compound is available in collyrium form under the name of Ophtazol.

Matrasil

For the treatment of pyelitis, cystitis and urethritis due to infections by *Streptococcus faecalis, B. proteus, E. coli,* or *Ps. pyocyaneus;* and for prevention of such infections following surgery of the genito-urinary tract, there is being marketed a tablet containing 0.5 Gm. and a solution containing 30 per cent of para-sulfanilamide-salicylic acid, a compound of sulfanilamide and *p*-amino-salicylic acid. The tablets are given orally and supplemented by irrigation of the urinary tract by neutral solutions of the sodium salt. Under the name of Matrasil this product is available from Ward, Benkinsop and Co., Ltd. of England.

Milibis

Bismuth glycolylarsanilate has been shown to possess high amebicidal potency. Amebic dysentery was once considered to be only a tropical affliction but it is now known that it is world-wide in prevalence. In the United States the disease is most prevalent in the west and south central states. A course of therapy of the drug is usually 2 tablets (0.25 Gm.) 3 times a day for 7 days. The cure rate has been stated as being as high as 90 per cent.

Toxicity tests revealed that this drug in a daily dose of 75 mg./Kg. for five days cleared 10 hamsters of amebiasis infection. Ten times the effective dose given for five days caused no signs of toxicity in these animals, an observation in striking contrast to the toxicity of effective doses of other amebicides.

Bismuth glycolylarsanilate is marketed as Milibis by Winthrop-Stearns, Inc.

Nisulfazole

A new sulfonamide, *p*-nitro-N-(2-thiazyl) benzenesulfonamide (Nisulfazole), has been used in a 10 per cent suspension in acute cases of ulcerative colitis when sigmoidoscopic examination showed that only the rectum and lower colon were involved. The dosage employed was 1 to 2 ounces 8 to 12 times daily given rectally. When it was shown that the entire colon or more was involved 4 to 6 Gm. were administered orally each day in addition to the rectal therapy. The suspension spread well and coated the mucosal surface of the rectum and colon for a period of 2 to 6 hours. Nine patients in the active phase showed rapid improvement but 1 relapsed several months after treatment had been stopped and did not respond to the drug following the relapse. In most cases continuing therapy was required to maintain improvement. Of 10 patients in the active phase of the chronic stage 7 showed lasting improvement but 3 had intermittent exacerbations and remissions of varying severity. Nisulfazole had little or no effect on 4 patients who were in the polypoid hyperplastic stage of the chronic phase. Two patients showed persistent nausea which required the discontinuation of oral therapy.

Promacetin

Leprosy is another one of the many diseases which more or less defies therapy. In recent years the sulfones have been used with some success. Now another sulfone, formerly known as internal antiseptic 307, is being tested. Chemically this white crystalline compound is sodium 4,4′-diaminodiphenylsulfone-2-acetylsulfonamide. It is soluble in water at room temperature to the extent of 3 per cent.

The drug was given orally at meal times in initial dosages of 0.3-0.5 Gm. Every 2 weeks the dose was increased by this amount until a maximum of 3-4 Gm. daily was attained. No severe acute toxic symptoms were observed in the 27 patients given the drug for 16 months. Uniform and sustained improvement occurred in the lesions of the skin and mucous membranes.

Lesions which had responded to sulfone therapy but had become stationary and residual showed further clearing. Under the name of Promacetin this compound is being investigated by Parke, Davis and Co., Inc.

Sodium Pentachlorophenate, Copper Pentachlorophenate

Schistosomiasis is considered to be the world's number three health problem following after malaria and tuberculosis. It is estimated that 115,000,000 people throughout the world are affected. In Egypt 75 to 80 per cent of the entire population is infected. The economy and production of the country are believed to be reduced by one-third as a result.

Recently, the National Institutes of Health of the United States Public Health Service reported that sodium pentachlorophenate and copper pentachlorophenate are effective as snail-killers. By ridding the affected areas of the snails it is believed that the cycle in schistosomiasis can be broken. The disease is caused by a kind of flat, leaf-shaped worm called a fluke which spends part of its life cycle in the body of certain fresh water snails. Humans who bathe, drink, wade or do laundry in water containing these snails or the larval form of the flukes are apt to contract the disease. The flukes produce their eggs in the human body and these eggs in turn get back into the water either directly from humans using the water or via sewage.

Excellent results with these 2 chemicals in killing snails have been reported in tests in swamps, lily ponds, roadside ditches and backwash river waters in Puerto Rico. It is believed that the chemicals will have to be applied only 1 or 2 times a year. However, further studies on this subject are being conducted in Liberia. Toxicity studies of sodium pentachlorophenate and copper pentachlorophenate have shown that they do kill catfish, guppies and eels, but not crayfish. So far as is known they do not harm humans or cattle drinking or bathing in the water.

Sulfabenamide

Another new drug is being tested for its value in leprosy. Chemically it is 4-N-capro-amidobenzene-sulfone-hydroxamide (N-(p-hydroxysulfamyl-phenyl) caproamide). Under the name of Sulfabenamide it is being investigated by Sharp and Dohme, Inc.

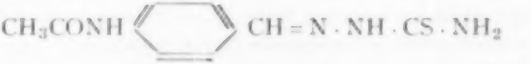
Thiodiamine

In India a new drug, thiodiamine, has been extracted from the bark of the *Crataeva Roxburghii* tree and is being used in the therapy of cholera.

Thiosemicarbazones

Recently interest has developed in an entirely new series of compounds showing value in the therapy of tuberculosis. These compounds had been investigated thoroughly in Germany and the one showing the best results, TB1/698 had already been tested clinically on approximately 7000 patients. One of the original German investigators was none other than Dr. Gerhard Domagk, Nobel Prize Winner and the discoverer of the first sulfonamide.

Chemically this new compound is p-acetylaminobenzal-thiosemicarbazone and is not related to streptomycin, dihydrostreptomycin or PAS. It is a bitter tasting, yellow, microcrystalline powder with a molecular weight of 236.28. It melts and decomposes at approximately 230° C. TB1/698 is soluble in water only to the extent of 0.0088 per cent at 20° C. and 0.0172 per cent at 37° C. It is sparingly soluble in alcohol, acetone and chloroform, more soluble in glycerin and alkaline solutions such as ethanolic or methanolic sodium hydroxide solution.



In vitro tests have shown that TB1/698 inhibits the growth of the tubercle bacilli in concentrations as low as 1:200,000 or 5 micrograms per cc. Para-aminobenzoic acid does not suppress this effect as it does with the sulfones and PAS.

Tests with guinea pigs and mice showed that TB1/698 was capable of suppressing experimental tuberculosis. In a comparison on animals with PAS it was found that TB1/698 required only 1/50 of the dose to exert a comparable effect.

Believed to have a primary effect upon the tubercle bacillus this compound not only inhibits the growth but it also produces morphologic alterations in the bacillus such as abnormal size and granular degeneration, formation of thread-like and coccoid forms and impaired ability to take acid-fast stains.

The sulfur atom in the molecule is responsible for the tuberculostatic activity as shown by the loss of this activity when the

sulfur atom is replaced by an oxygen atom. The para position of substitution in the benzene ring also possesses an effect on the activity. In the body TB1/698 breaks down into the benzaldehyde and thiosemicarbazone portions which are inactive and toxic. Therefore, they are not responsible for its action.

Studies of absorption and excretion of chemically similar thiosemicarbazones have shown that they are rapidly absorbed into the blood stream after oral administration. Within one hour after ingestion the serum concentration attains a maximum. Since only traces are observed in the urine most of the drug is believed to be destroyed in the body.

As with the other antitubercular drugs TB1/698 is to be used alone or in combination with other agents such as streptomycin, dihydrostreptomycin or PAS. In the German clinical trials it has been found effective in laryngeal and intestinal tuberculosis, in lupus vulgaris, in pulmonary and genito-urinary tuberculosis, and in tuberculous empyema. Somewhat encouraging results have been found in bone and joint tuberculosis. In miliary and meningeal tuberculosis it has shown poor results. Consequently, in these conditions streptomycin remains the drug of choice. However, TB1/698 may be administered in addition to parenteral and intrathecal administration of streptomycin.

Experiments have shown that TB1/698 may have value in delaying the development of resistance by the bacilli.

TB1/698 can be administered for a considerable length of time which may make it of value in the preparation of patients for operations thus reducing the danger of post-operative complications. This property also may make it of value in treating chronic types of tuberculosis in which streptomycin or dihydrostreptomycin are contraindicated. Recommended doses are as follows:

Adults

1st week, 50 mg. orally, per day, in divided doses
2nd week, 100 mg. orally, per day, in divided doses
Then, 200 mg. orally, per day, in divided doses

Children

1st week, 0.5 mg./Kg. of body weight, daily
2nd week, 1.0 mg./Kg. of body weight, daily
Then, 2.0 mg./Kg. of body weight, daily

The dosages as recommended in the table are set up with the purpose in mind of keeping any accompanying gastro-intestinal distress as a minimum. In the very beginning of therapy there may be nausea, anorexia and occasionally vomiting but such symptoms usually subside rather quickly even though therapy is continued. These side effects also may be reduced or eliminated by giving the drug with meals and also administering small quantities of barbiturates. Antacids and antihistaminics also may be helpful.

The daily dose may be given at one time or it may be administered in 2 or 4 divided doses. Because it is not essential to maintain constant serum concentrations of the drug around-the-clock administration is not required.

Although TB1/698 is generally given orally it can be administered in other forms. For empyema cavities, large lung cavities and draining fistulas a suspension of 10 to 20 per cent of the powdered drug in distilled water or sterile saline may be instilled in 1-2 cc. quantities. The powdered drug may be administered by insufflation into the larynx and bronchial tree.

Viacutan

Dinaphthalene methane silver disulfonate in 1 per cent aqueous solution with a pH of 4.5-5 is being marketed for the treatment of trichomoniasis. It contains a wetting agent to assist spreading and a water-soluble yellow dye to indicate the areas treated. It is known as Viacutan and is available in England.

ANTISEPTICS

Bactine

A new antiseptic, bactericide, cleanser-deodorant and fungicide has been made available, the active ingredients of which are di-isobutyl-cresoxy-ethoxy ethyl-dimethyl-benzyl ammonium chloride, polyethylene glycol mono-iso-octyl phenyl ether, chlorothymol, alcohol 4 per cent. This product is a clear, colorless, non-staining liquid with a clean, fresh odor and can be used as a general antiseptic for office, hospital, personal and home use. Known as Bactine it is being marketed by Miles Laboratories, Inc.

Iodine Solution

Iodine has been established for many years as an efficient and versatile antiseptic. The solvent for the iodine has varied over the

years but most commonly is found to be alcohol, water or a combination of the two. However, the use of alcohol causes irritation and pain when the antiseptic solution is applied to open wounds. On the other hand, an increase in the proportion of water increases the hazard of freezing of the solution under conditions of low temperature storage or shipping, a hazard manifested by the damage to surrounding materials should the bottles of solution freeze and crack.

Recently, Gershenfeld and Witlin suggested a solution of iodine composed of 2 per cent iodine, 2.4 per cent sodium iodide, 25 per cent propylene glycol and distilled water. This solution has a high bactericidal efficiency, a free iodine content equivalent to the present-day iodine tincture, a low freezing point, and it does not sting nor irritate the skin. It also has a desirable adhesiveness to human skin and mucous membranes.

This solution is applicable not only to human and veterinary use but in food utensil sterilization, for the disinfection of thermometers, for water for human consumption, and in the disinfection of swimming pools.

Oronite Quaternary ATM-50

N-alkylbenzyl-N, N, N-trimethylammonium chloride is a surface-active agent and a germicide. A 50 per cent aqueous solution is nearly colorless and odorless. Determined by the modified F. D. A. method for germicidal activity, the phenol coefficient is approximately 250 (100 per cent basis). As a cationic surface-active agent it has a very high activity reducing the surface tension of water to 38.4 dynes per cm. at 0.001 per cent concentration and 29.2 dynes per cm. at 0.01 per cent. N-alkylbenzyl-N, N, N-trimethylammonium chloride is nontoxic and nonirritating to the skin and is compatible with most nonionic surface-active agents and with inorganic salts, thus allowing for the preparation of various dry, free-flowing detergent sanitizer compounds.

The Oronite Chemical Co. is making this compound available under the tradename, Oronite Quaternary ATM-50.

ANTISPASMODICS, MUSCLE RELAXANTS

Dihydro-beta-erythroidine

Parkinsonism or paralysis agitans is a disease which manifests itself by muscular rigidity accompanied by tremor. Atropine and

related compounds have been used therapeutically in order to control the rigidity. Improvement was obtained in most cases but after reaching a certain level no further improvement was attained. Recently dihydro-beta-erythroidine has been used in conjunction with atropine to augment the results. The compound is the hydrogenated alkaloid obtained from the genus *Erythrina L.* and has a curare-like action. When given alone it has little or no effect on patients with Parkinsonism but when combined with atropine the effect is augmented.

The optimum therapeutic procedure is to administer atropine in gradually increased dosage until the maximum clinical response is obtained. When this base-line improvement is reached and maintained then dihydro-beta-erythroidine is administered in oral doses of 50 mg. four times a day. Additional improvement is usually evident within 1 to 3 weeks and a maximum improvement is reached within a month. The withdrawal of the new drug causes a recrudescence of symptoms and readministration causes improvement again. The only improvement is on the rigidity with little or no effect on the tremor.

Toxic symptoms were confined to gastro-intestinal disturbances, blurring of vision and dizziness. In most of the 11 cases in which they appeared these were mild and transitory. No other systemic disturbances were observed in the 24 patients subjected to this treatment.

Khellin

Khellin, a smooth muscle relaxant derived from the plant *Ammi visnaga* Lam (Arabic: khella), indigenous to the Eastern Mediterranean and Arabian areas, is a compound for prophylactic use in the relief of angina pectoris and chronic bronchial asthma. Most of the reports in the literature refer to work done with a mixture of active principles, chiefly khellin, derived from the plant. In these reports the mixture is loosely called khellin. The name khellin, however, should be reserved for the particular pure chemical compound in the mixture, *i.e.*, 2-methyl-5, 8-dimethoxy-furanochromone. Khellin is thus to be differentiated from two other derivatives from *Ammi visnaga*, namely visnagin and khellol glucoside. The name visammin has also been used to designate khellin and the name khellin has been used for the compound usually called khellol glucoside.

Khellin relaxes all smooth muscles so far tested, apparently largely by direct action on the muscle itself. It acts not only on untreated muscle but also on smooth muscle contracted by histamine or acetylcholine.

Because of its bitter taste, which once was a criterion in using plant extracts as medicinals, *Ammi visnaga* has been used as a remedy in Eastern Mediterranean countries for centuries. In 1934 preparations of this plant in the form of a 1 to 10 tincture and 1 in 40 decoction were introduced into the Egyptian Pharmacopeia and recommended as an antispasmodic in renal colic. Since then, pharmacological reports of khellin's dilating effect on the coronary arteries have led to clinical studies of its effect in angina pectoris.

The common cause of the chest pain in angina pectoris is believed to be impairment of the blood supply to the heart as a result of arteriosclerosis. An acute attack is probably always associated with some spasm of the coronary vessels as well. Because of these considerations and the immediate relief which occurs with nitroglycerin, the place of coronary dilators in the treatment of angina pectoris is firmly established. Pharmacological and clinical reports now indicate that in khellin a really effective, long-acting agent has been found for the prophylaxis of angina pectoris.

Khellin also has been given limited trial in bronchial asthma, as a prophylactic drug, though epinephrine remains the most effective agent for relieving the acute attack. Epinephrine is limited by its evanescent action, the way it is administered (parenterally), its pressor effects on the circulation, and the fact that some asthmatics become "epinephrine fast." In an Egyptian trial of khellin in asthma, 41 out of 45 patients got relief from intramuscular injections of 200-300 mg. of khellin.

Khellin also has been reported safe and effective in the symptomatic treatment of whooping cough. The distressing, often debilitating paroxysms occurring in this infection are a result of mucous plugs obstructing the bronchioles. Bronchial and bronchiolar dilators apparently relieve this condition because obstruction is lessened and the inflammatory secretions are more easily removed.

In its present marketed forms khellin is available in 20 and 40 mg. tablets, for oral administration. Dosage is variable, dependent upon two factors: (1) a process called khellinization, and (2) side effects. Khellin has a cumulative effect, in the manner of digitalis.

Initial dosage for angina pectoris is one tablet (40 mg.) 3 times a day, after meals, though in some cases 4 a day are required. Accumulation of khellin at the therapeutic level (khellinization) should be obtained in 3-7 days. In cases where untoward effects develop early, khellinization at a lower level is needed. It should be withdrawn for 2-3 days, then one tablet given daily for a week, after which the daily dose can be increased one tablet, at weekly intervals, until therapeutic effect is attained.

Thereafter, a maintenance dosage should be determined. Three tablets (40 mg.) a day produce maximum therapeutic benefit for many patients, but untoward effects tend to appear or increase with cumulation, usually after 4-7 days. In these cases dosage should be dropped first to 2 tablets a day, then to one. Most patients can take either 3 or 2 tablets per day for considerable periods of time.

Dosage procedure for bronchial asthma is substantially the same as for angina pectoris.

Khellin has recently been marketed in the United States under the trademark Eskel by Smith, Kline and French Laboratories. Eskel is a mixture of active principles, chiefly khellin, derived from the plant. Pure crystalline khellin is marketed as Ammivin by The National Drug Co.

Panparnit

Panparnit or caramiphen hydrochloride is one of the newer synthetic drugs for reducing rigidity and tremor in Parkinson's disease. It was previously known as Parpanit. This drug acts effectively in the condition without the disagreeable side effects of conventional therapy with belladonna alkaloids—dry mouth and disturbances of vision. The diminution in rigidity obtained results in greater freedom and speed of movement and greater ease in feeding and talking. This drug appears to act by blocking the proprioceptive impulses arising in muscles and joints. The dosage administered is regulated according to the patient. Panparnit is marketed by Geigy Co., Inc.

Procaine

For many years procaine has been used to produce anesthesia. However, in recent years new uses for this drug have been discovered. Within the last six months it has been reported that procaine

given orally is effective in relieving pyloric spasm. Just as with so many other discoveries the effectiveness of oral procaine in this condition was accidentally discovered during an intensive investigation of the mechanism of the pyloric reflex. In a period of 4 years Roka and Lajtha examined fluoroscopically several hundred patients. They found that normally when the stomach is empty the pylorus is open and that it closes when some stimulating substance passes into it from the stomach. The stimulating substance may be food or the diagnostic medium. Thus the basic stimulus for closing the pylorus physiologically is apparently a local irritation of the wall. Therefore, if an anesthetic could be given which would affect the local nerve endings so as to block conduction, spastic closure of the pylorus might be inhibited.

Since procaine hydrochloride is not very toxic in dilute solution and it does possess the property of blocking nerve conduction it was selected for the tests. One hundred cc. of a 1 per cent solution was the dosage given. The patient, in a sitting position, was instructed to drink slowly this quantity of solution over a period of 4-5 minutes. After 5 to 15 minutes later the pylorus was observed to determine its movements. It was found that in over 150 normal individuals the pylorus became almost completely paralyzed within 10 minutes. Complete atonicity was produced and the contrast medium passed through without any hindrance. The stomach movements were normal in every respect. The procaine also prevented reflex response to any local mechanical irritation. Relaxation of the pylorus was achieved in patients who were considered hopeless and resistant to all therapy. In a study of more than 100 cases known to have a spastic pylorus and a stomach which emptied slowly with a constant residue the sphincter was observed to relax promptly after oral administration of procaine. If the pyloric canal was obstructed by cancer or by scar tissue from a healed ulcer oral procaine had no effect.

Oral procaine also prevented vomiting in 11 cases of gastric ulcer. In 5 patients with cancer of the stomach normal feeding was restored resulting in relief of malnutrition and hypochloremia. Surgery could then be performed.

The effect of the procaine lasts for 2 to 3 hours. It can be given in 1 per cent solution in doses of 50 to 100 cc. twice a day for several days without any untoward reactions.

d-Tubocurarine Chloride

An essentially chemically pure form of d-tubocurarine chloride has been announced by the Transandino Company, Palo Alto, Calif. The purity of this form makes possible the adjustment of therapeutic formulations with previously unobtainable accuracy. Content can then be checked by physico-chemical means rather than bio-assay methods. This new form of the drug also exhibits a higher margin of physiological safety than previous forms of tubocurarine.

ANTITHYROID DRUGS

Tapazol

A new antithyroid drug, 1-methyl-2-mercaptoimidazole, has been found to have a pronounced effect on iodine accumulation in the thyroid in quantities as small as 0.5 mg. Since it is an imidazole derivative it has a 5-membered ring. The antithyroid drugs now available have a six-membered ring. When compared with thiouracil, methylthiouracil, propylthiouracil and 2-mercaptoimidazole, 1-methyl-2-mercaptoimidazole was found to possess greater action than any of these. It is rated as 100 times as potent as thiouracil. However, in clinical studies it is observed to be 20 to 50 times more potent than thiouracil. The optimum dosage is 2 to 5 mg. every 8 hours. No toxic reactions have been observed following its use.

Eighteen patients with hyperthyroidism were selected for the clinical trials. Of the three patients with toxic diffuse goiter 2 showed remission of symptoms in about 8 weeks with a dosage of 2 mg. every 8 hours, and 1 in about 8 weeks with a dosage of 5 mg. every 12 hours. Two mg. every 8 hours, 5 mg. every 12 hours and 2 mg. every 12 hours were the respective dosages necessary to effect remissions in 3 patients with toxic adenoma in 5 to 6 weeks. Ten patients given 1 mg. of the new drug instead of 25 mg. of propylthiouracil experienced satisfactory control of symptoms. In the 2 patients with mild relapses the symptoms were controlled by a dosage of 2 mg. every 12 hours. It required 57 days in the patient with a relapse after 1 year and 51 days in the one with a relapse after 6 months.

1-methyl-2-mercaptoimidazole appears to resemble propylthiouracil in its antithyroid effects but it has about 25 times greater potency. Further investigation is necessary to obtain a true picture

of this new drug and any possible toxic reactions it may have. Thus far none have been observed. Under the tradename of Tapazol it is being investigated by Eli Lilly and Co.

ARTHRITIS

Acetoxy-Pregnenolone

Another steroid which was recently described as being effective in the therapy of rheumatoid arthritis is Δ^5, pregnene, 3 beta, 21 diol-20 one-21 monoacetate. It is synthesized from a sapogenin derived from the roots of wild Mexican plants known as yams or from cholesterol from animal, vegetable or other sources.

In some cases this compound is more effective than some of the other steroid hormones. It is marketed as Acetoxy-Prenolon by Schering Corporation and as Artisone Acetate by Wyeth, Inc. It has been used successfully in the treatment of rheumatoid arthritis, lupus erythematosus, inflammatory rheumatism, osteoarthritis, other collagen diseases, menometrorrhagia, and certain ophthalmologic conditions.

ACTH and Potassium Diet

Tests on rats have shown that a high potassium diet may offset the bad effects of ACTH. However, this may not be true in man since rats are physiologically not the exact counterparts of men. ACTH stimulates the adrenal cortex resulting in drastic changes in physiological chemistry. In the destruction of body tissue nitrogen and potassium are liberated and excreted in large quantities and a loss in weight occurs. No loss of weight and no loss of nitrogen occurred when rats were given a high potassium diet followed by injections of ACTH. Further investigation is necessary since it has not been determined whether the potassium also interferes with the therapeutic effects of ACTH.

Cortisone and Insulin

The cost of therapy and the small quantities of cortisone available have served as limiting factors to its use. However, a recent discovery of synergism between insulin and it may help to ease the situation. Earlier laboratory studies of the action of steroid hormones on the adrenocortical enzyme system *in vitro* resulted in the

development of the hypothesis that insulin might be a synergist to cortisone. Thus more complete utilization of cortisone by the body tissues could be accomplished and the same clinical effect could be achieved with smaller doses. Cortisone is known to bring about the synthesis of a tissue carbohydrate and it was thought that insulin might increase this activity by making activation-products of glucose readily available to the tissues without necessitating conversion from amino acids. By such a reduction of the usual dose of 100 mg. daily not only will the cost of therapy be decreased but also the undesirable side effects of cortisone might be eliminated.

Recently this hypothesis was tested clinically on 12 patients with rheumatoid arthritis. In these patients the duration of the disease was 6 weeks to 20 years, and its progression in stages I to IV; there were 9 females and 3 males, their ages 28 to 67 years. Following routine appraisal studies the patients were given 12.5 to 50 mg. of cortisone acetate in aqueous suspension and 20 to 60 units of plain insulin in aqueous solution daily by injection in single or divided doses during successive ten-day periods. No clinical improvement was observed in 10 days in 4 patients receiving 12.5 mg. and 20 units, respectively. Of 8 patients receiving 25 mg. and 40 units for ten days, 6 exhibited a rapid fall in sedimentation rate and 4 had definite signs of clinical reversal. In order to arrive at more rapid clinical changes, all 12 patients were advanced to 50 mg. and 40 units for ten days, during which time 10 progressed to normal sedimentation rates and 8 to well-marked clinical reversals, grade I and II. It is believed, however, that further clinical benefit was available at the 25 mg., 40 unit dosage.

During the 30-day period none of the usual side effects from cortisone was observed with the possible exception of 1 patient who developed edema of the ankles. Hypoglycemia caused little difficulty, being readily controlled when it occurred, and was not related to the degree of response. The patients gained 4 to 29 lbs. in weight.

Although further investigation of this synergistic effect is necessary, the preliminary results accomplished open the way for numerous other possibilities in applying the principle observed.

Desoxycorticosterone Acetate and Ascorbic Acid

A combination of desoxycorticosterone acetate and vitamin C given parenterally has shown improvement in most patients with chronic forms of arthritis. The DeCourcy Clinic recently confirmed

reports from other clinics here and abroad. The combination has been found particularly effective in patients in the acute phase of rheumatoid arthritis. A dose of 5 mg. of desoxycorticosterone acetate is administered intramuscularly followed within five minutes by one Gm. of ascorbic acid intravenously. Palliation of symptoms is obtained in a considerable number of degenerative joint diseases (osteoarthritis) similarly treated. As a result of the improvement physiotherapeutic and orthopedic measures can be more effectively applied. Some firms are marketing the two drugs separately whereas others have made them available in one ampul.

Glucuronolactone

To a series of 50 patients suffering from various types of arthritis glucuronolactone has been administered in syrup or tablet form. The dosage employed ranged from 10 to 15 gr., given 3 or 4 times a day. Therapy was continued from one week to a year with an average of about 2 months. The best results were obtained in the treatment of sciatica in which all 5 patients obtained complete relief or major improvement. The least benefit was obtained in the treatment of rheumatoid arthritis in 14 patients, only 5 of whom obtained major improvement. Major improvement was obtained in 2 or 4 patients with mixed arthritis, 2 of 2 with gout, 8 of 16 with osteoarthritis, 1 of 2 with the shoulder-hand syndrome, 1 of 2 with Marie-Strumpell disease and 1 each having infectious arthritis and palindromic arthritis. All of the patients had previously received other types of arthritis therapy without lasting benefit. The benefits from the glucuronic acid therapy in the cases of rheumatoid arthritis often seemed to cease with the end of therapy. The patients with osteoarthritis who received the most benefit from this therapy had had the disease for less than one year. The only side effects noted were in three patients and consisted of flushing of the face, diarrhea, and gastric upset.

Another report stated that glucuronolactone has brought improvement to an average of about two-thirds of the patients with various rheumatic disorders in whom it has been tried. In one series of 256 cases 34 per cent showed marked improvement, 34 per cent showed moderate improvement, and the remaining 32 per cent showed little or no improvement. Glucuronic acid and its various salts have been found to have very low toxicity.

Glucuronolactone, the crystalline gammalactone of glucuronic acid, appears to act by direct attack upon the factors responsible for the arthritic process. It exerts little or no analgesic action, the clinical improvement being produced through its influence upon the metabolism of bone, tendons, and cartilage.

This drug is now produced synthetically in tablet form and is being made available in limited quantities for medical investigation under the name Glucurone by CSC Pharmaceuticals, Division of Commercial Solvents, Inc.

Medinova

Arthritis deformans, spondylosis deformans, polyarthritis acute and chronic, infectious arthritis, muscular rheumatism have been treated effectively in some cases by a product combining salicylamid and ascorbic acid. Known as Medinova this product is being marketed in Europe.

Oral Cortisone

Cortisone was discussed in last year's review, so that it will not be considered in detail here. However, the recent reports of its effectiveness when given orally necessitates its mention. Considerable research has been conducted on this drug in the past year.

The dosage of cortisone intramuscularly is 300 mg. the first day, 200 mg. the second and 100 mg. daily thereafter. Consequently, when the drug was prepared in 100 mg. tablets for oral administration the dosage given was the same. In two patients the maintenance dose was increased to 200 mg. daily after they had been given 100 mg. for a few days. The results in the patients studied revealed that cortisone is effective orally and produces results comparable to those brought about by parenteral administration. This new development will be of considerable value in treating patients with a chronic illness such as rheumatoid arthritis. However, the therapy must be carefully controlled so that use of such a potent substance is not abused.

DENTAL AID

Thistledown Seaweed

Practical trials by British dentists have shown that thistledown seaweed is effective in stopping gum bleeding after tooth extractions. One application is all that is necessary in most cases and the substance disappears without any trace in about an hour after applica-

tion. This seaweed, found on the North Scottish coast, consists chiefly of sodium alginate. One of the British textile firms processes it into powder form and then dissolves it in water to form a thick solution. This in turn is filtered and forced through a series of hair-fine jets in a platinum cap. The threads are passed into a solution which converts them into insoluble calcium alginate. These crude fibers are then tested, dried and woven into gauze by ordinary textile machinery. After partial reconversion to sodium alginate and careful neutralization the material is dried and tested. Unlike some products used for stopping bleeding this material does not affect penicillin. It is hoped that it may be used in general surgery as well as in dentistry. In the latter field, at present, a crown of buff-colored featherweight material is inserted into the tooth socket and the bleeding stops. The gauze disappears.

Because the alginates are so light in weight it requires 35 tons of seaweed to make 1 ton of sodium alginate.

DIABETIC AIDS

Insulin Mixtures

The use of insulin mixtures in controlling diabetes was first reported in 1937. By mixing regular insulin in the proper proportion with protamine zinc insulin it was found that only one injection a day was necessary. In addition this intermediate type of action resulted in the elimination of most of the glycosuria during the day, a common occurrence when protamine zinc insulin alone is used. Further investigation was carried out to determine the exact activity of various mixtures. It was found that it was possible to prepare mixtures of the two insulins which would give any desired intermediate action between the two in respect to promptness, intensity and duration of effect. Unfortunately any gains in intensity and promptness were achieved at the expense of prolongation of action and vice versa. Decisive intermediate effects could not be achieved until a mixture containing at least equal quantities of the two insulins was used. In cases of severe diabetes mixtures containing 2 or 3 times as much regular insulin as protamine zinc insulin were found to give better results. These mixtures apparently gave good intermediate effects because of the reduction in the quantity of protamine, zinc or alkaline buffer. From these tests it was evident that a different physical or chemical form was responsible for the intermediate effects rather than

the composite action produced by the simple fractions of soluble insulin and insoluble protamine zinc insulin. The clinical tests with these mixtures revealed that better results were obtained following the administration of one of them once daily than if the protamine zinc insulin or unmodified insulin was given alone or administered separately at the same time. Despite the efficiency of such mixtures there were difficulties encountered in mixing. Recently a new and simplified method of mixing has been reported to be successfully used. Under sterile technic a 25 gauge needle is inserted into each of the bottles containing the two types of insulin. The bottle of regular insulin is inverted, the needle applied to the syringe and the proper dosage withdrawn. Next the bottle of protamine zinc insulin is inverted, the same syringe applied to that needle and the dose of protamine zinc insulin is withdrawn. The needle and syringe are then withdrawn together and a small bubble of air drawn into the syringe. The syringe is tilted to mix the insulins, the air is expelled and the mixture is ready for injection. By means of a mechanically reproduced 8½ by 11 inch card illustrating these various steps the originator of this technic explains and demonstrates it to his patients in less than 2 minutes. The patient is given a copy of the card of instructions with the proper doses indicated for him written in the margin next to the respective bottles.

NPH 50

At the Mayo Clinic it has been the custom to give protamine zinc insulin only to patients requiring 20 units or less daily. Mixed insulins (1.5 to 3 units of regular insulin to 1 unit of protamine zinc insulin) are given to those requiring more than 20 units daily. The same objections as mentioned previously were encountered but the satisfactory control of the condition by this therapy overcame the objections. Clinical trials of a specially modified insulin have been conducted by the Mayo Clinic. Known as NPH 50 it is a neutral crystalline protamine zinc insulin and has an action intermediate between that of regular insulin and protamine zinc insulin. The prediction has been made that some preparation of insulin with an intermediate effect will eventually not only replace protamine zinc insulin and insulin mixtures but will improve and simplify the therapy of diabetes. There is some indication that NPH 50 may be the preparation.

The name NPH 50 is derived from N for neutral, P for protamine and H for Hagedorn who, along with Krayenbuhl and Rosenberg, developed the method for preparing the crystals of protamine zinc insulin used. The figure 50 is indicative of the approximate amount of protamine (0.50 mg.) used in preparing 100 units of the new insulin. These crystals are beautiful tetrahedrons having shiny faces and sharp, smooth edges. Under proper conditions they are quite stable and can be made into suspensions to which the regular insulin can be added without losing the quick action so characteristic of the regular soluble insulin.

Twenty diabetics were selected for the trials of NPH 50. These were all ambulatory and the severe diabetes was reasonably satisfactorily controlled by means of tailormade insulin mixtures. After 2 to 6 months a summary of the results revealed that tests for glycosuria in 9 cases (6 of which also required supplements of regular insulin) were more satisfactory and in 5 the tests were the same. Eighteen expressed the opinion that NPH 50 was more convenient and 17 thought it more satisfactory. No untoward reactions and no local or general allergic reactions were observed.

Overdosage of NPH 50 caused insulin reactions which were more easily recognized than are those induced by protamine zinc insulin. Hunger, perspiration, palpitation and restlessness were the symptoms most commonly encountered.

From this limited trial it was concluded that NPH 50 should prove to be at least as satisfactory as the insulin mixtures and even more so than protamine zinc insulin alone. Regular insulin also is needed in very severe cases but since it can be added to a suspension of NPH 50 without loss of potency it is more convenient than the syringe mixing of the regular and protamine zinc insulin. NPH 50 has an increased intensity of action in the first several hours after administration and when the need for insulin is increased while ingesting food. During the fasting hours of the night its activity is less intense but more prolonged.

NPH Insulin has been released by Eli Lilly and Co., Sharp and Dohme, Inc. and E. R. Squibb and Sons, Inc.

Sucaryl Sodium

The first non-caloric sweetening agent that can be used in cooking, baking and canning without loss of sweetness was made available recently. It is designed especially for use by diabetics and for

reducing and other diets which call for limitation of calories or carbohydrates. It has several advantages over saccharin, chief of which is the heat stability of the new product. Saccharin, the only other non-caloric sweetener on the market, decomposes in boiling solutions and as a result cannot be used to sweeten foods during cooking processes. Other points in favor of the new sweetener include the fact that when used in average household proportions, it has no trace of the bitter after-taste commonly associated with saccharin. According to the clinical investigators, this substance has been found to have a more natural sweetness, closely resembling that of sugar.

Chemically this new sweetener is sodium cyclohexyl sulfamate. It was discovered in 1937 by a young chemist who found its sweetening properties when he noticed a sweet taste in a cigarette he was smoking while working with the chemical. The effervescent tablets dissolve very quickly in warm solutions. Sodium cyclohexyl sulfamate is stable. One-eighth gram is equivalent in sweetening power to one teaspoonful of sugar. Until more clinical reports are available, it is recommended that adult patients limit their daily intake to eight tablets (1 Gm.). Patients suffering from severe kidney impairment should use only moderate amounts and under medical supervision.

Under the name of Sucaryl Sodium this product is available in tablet and liquid form from Abbott Laboratories.

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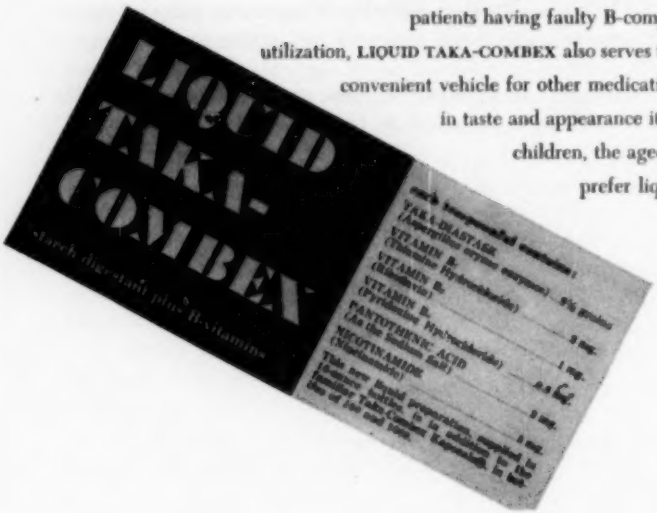

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